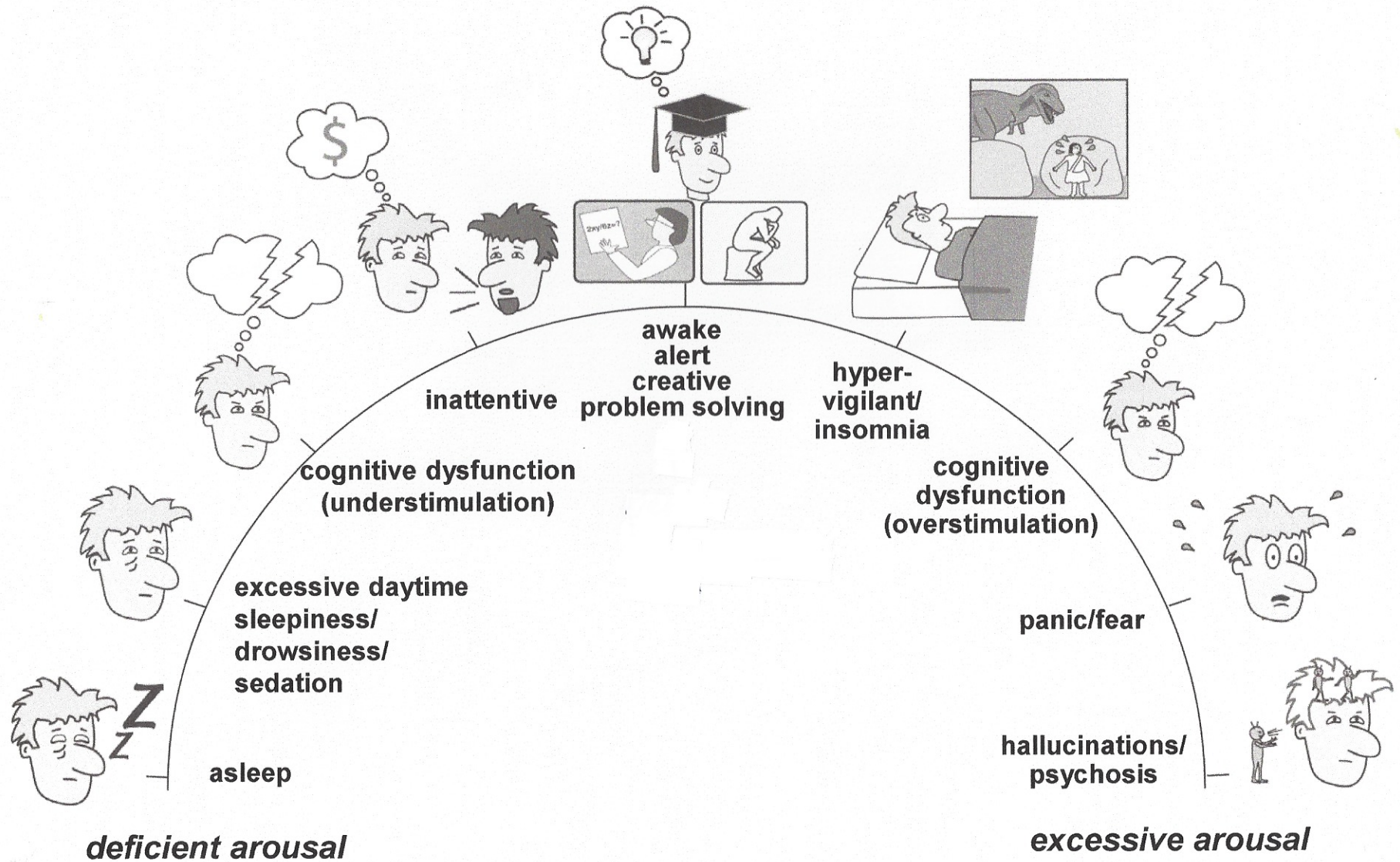
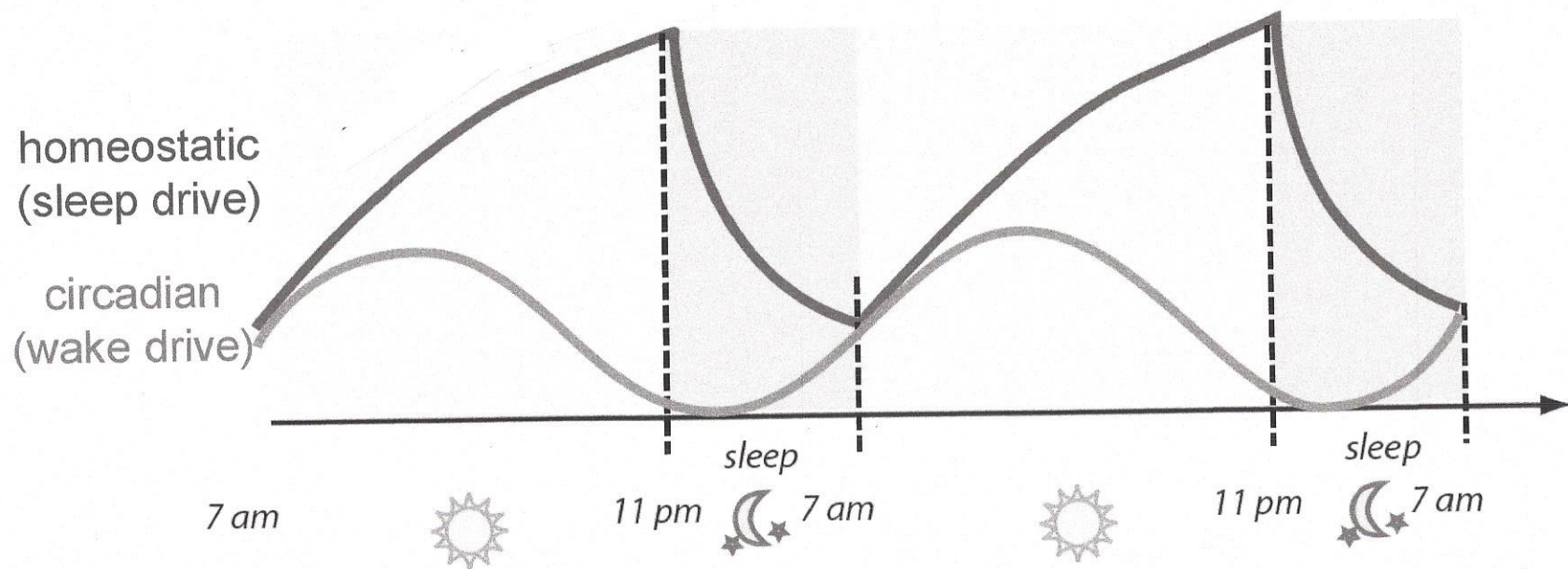


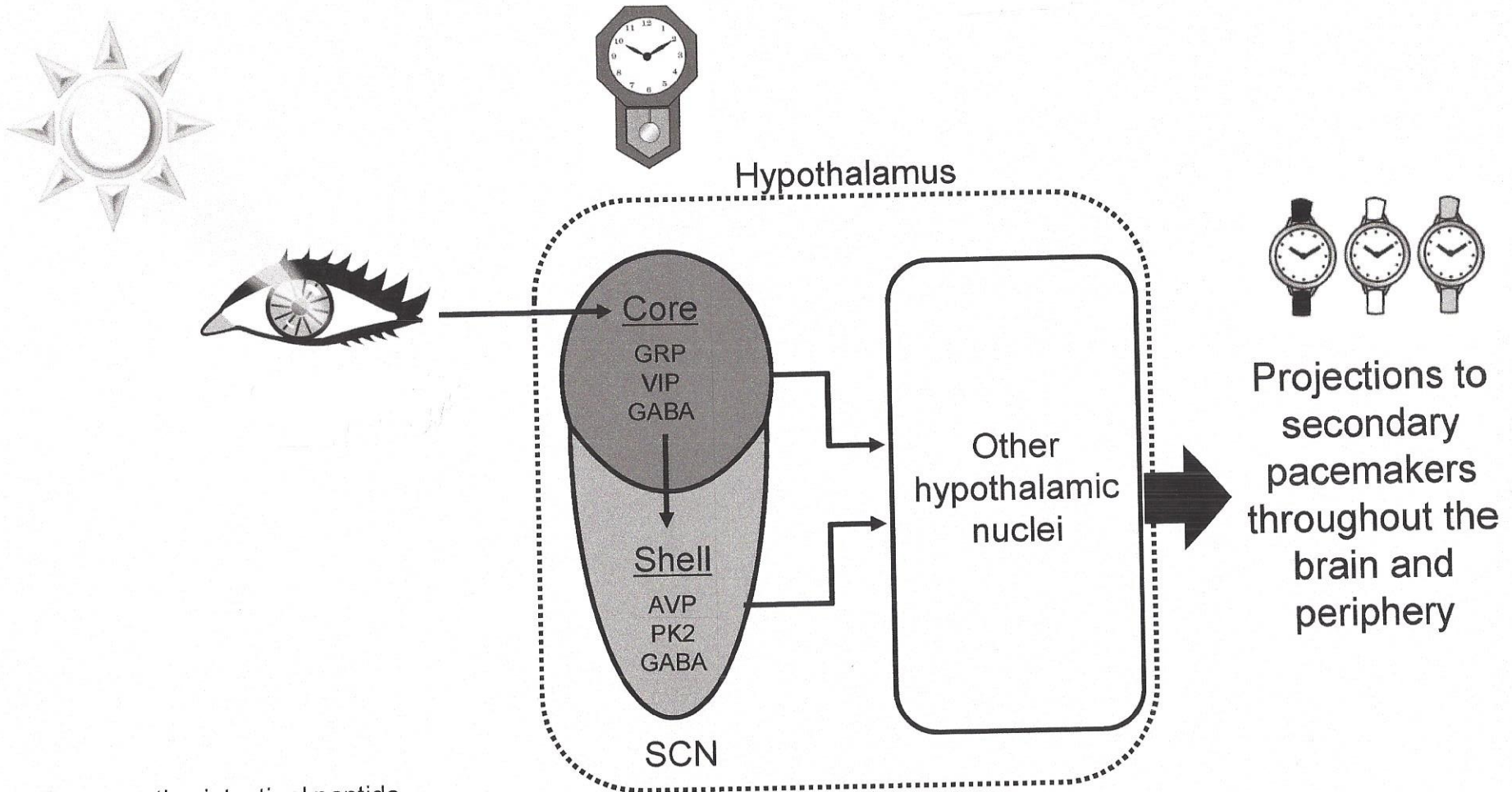
Arousal Spectrum of Sleep and Wakefulness



The Sleep/Wake Cycle



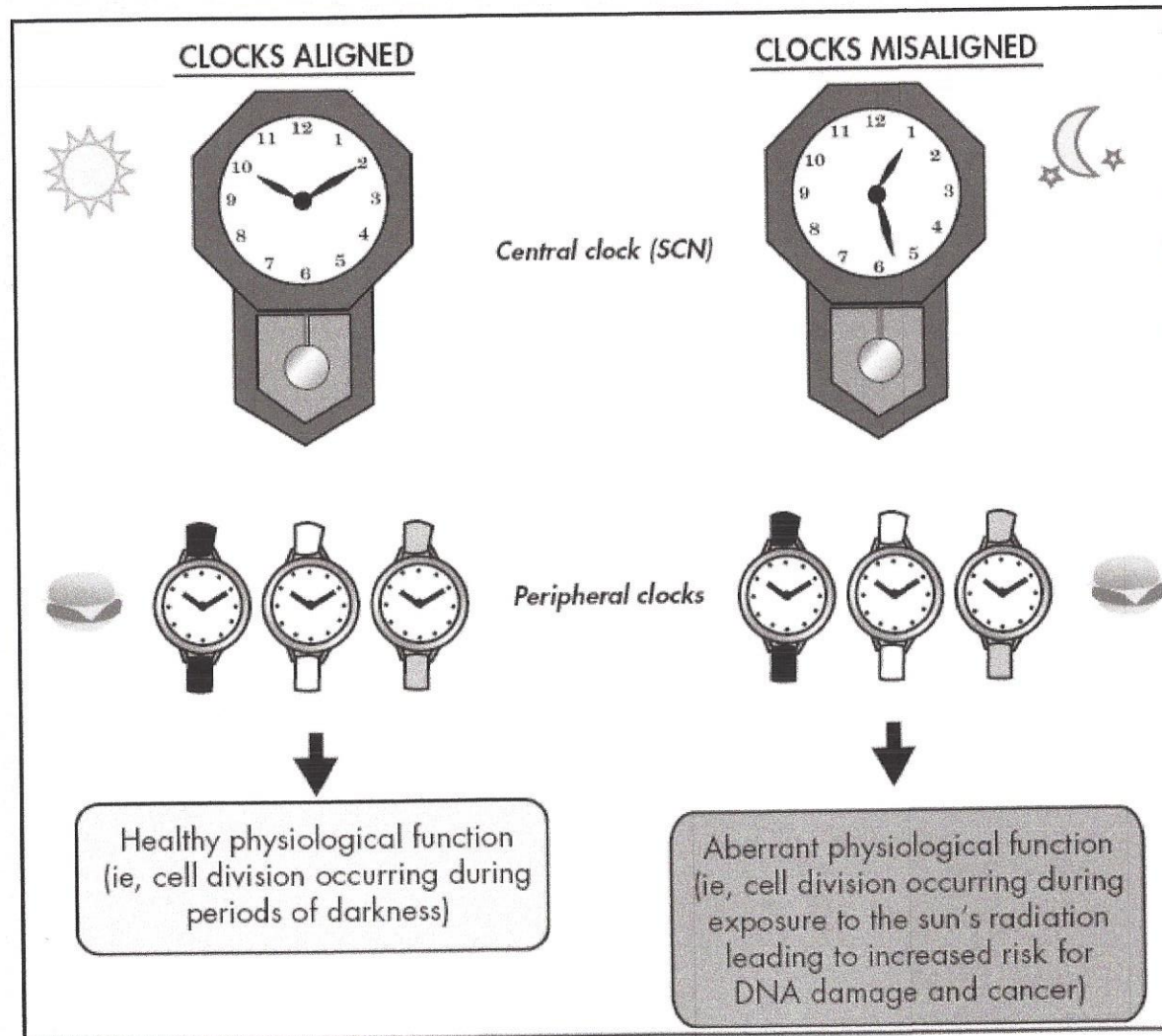
Suprachiasmatic Nucleus Control of Sleep



VIP: vasoactive intestinal peptide
GRP: gastrin-releasing peptide
AVP: arginine vasopressin
PK2: prokineticin 2

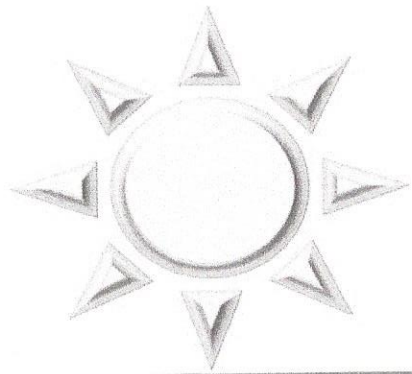
Brancaccio et al. J Neurosci 2014;34(46):15192-9; Colwell. Nat Rev Neurosci 2011;12(10):553-69.

Misalignment Between Central and Peripheral Clocks



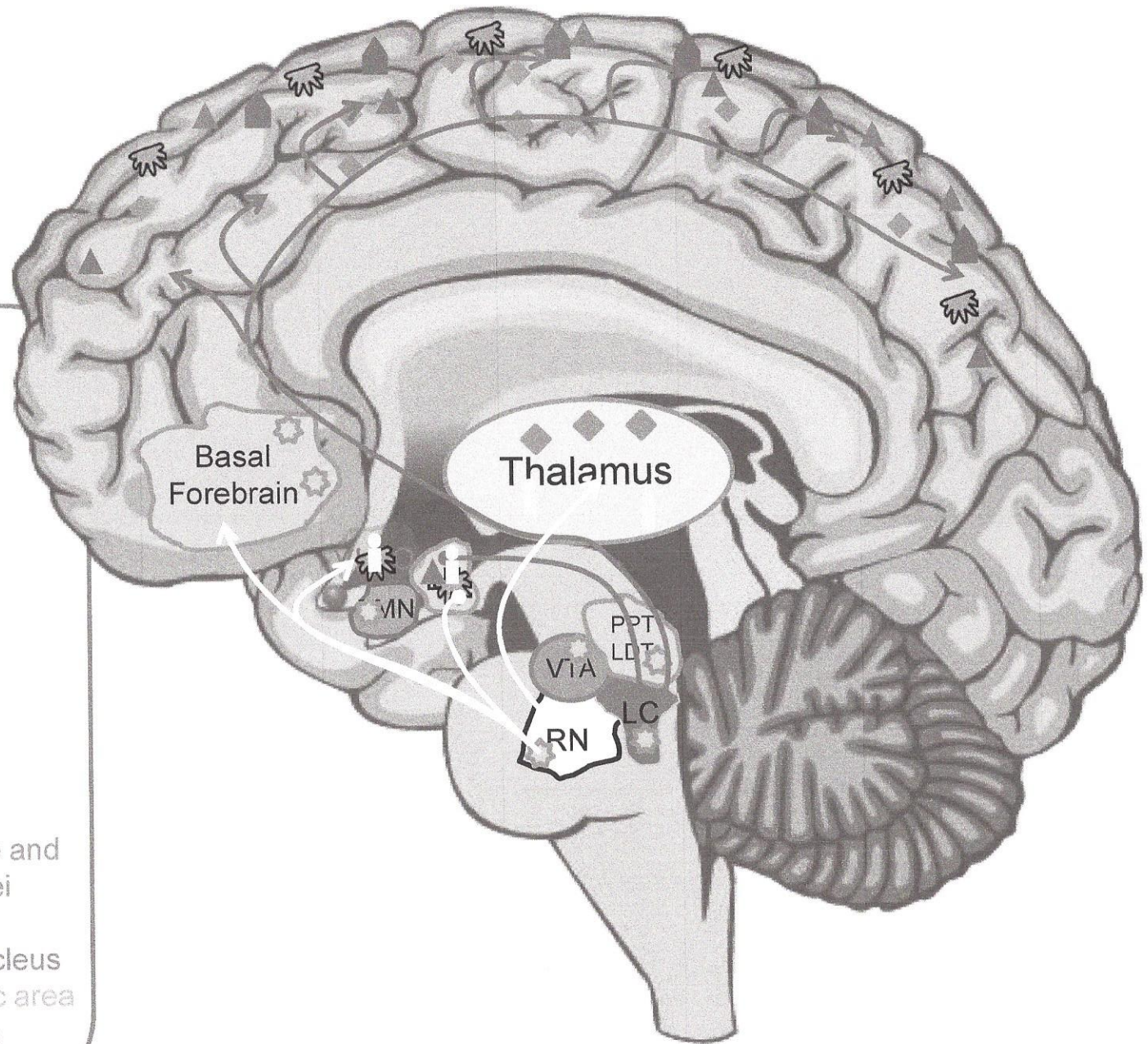
Green et al. Cell 2008;134(5):728-42;

Oosterman et al. Am J Physiol Regul Integr Comp Physiol 2015;308(5):R337-50.



-  GABA/Galanin
-  Hypocretin
-  Acetylcholine
-  Dopamine
-  Norepinephrine
-  Serotonin
-  Histamine

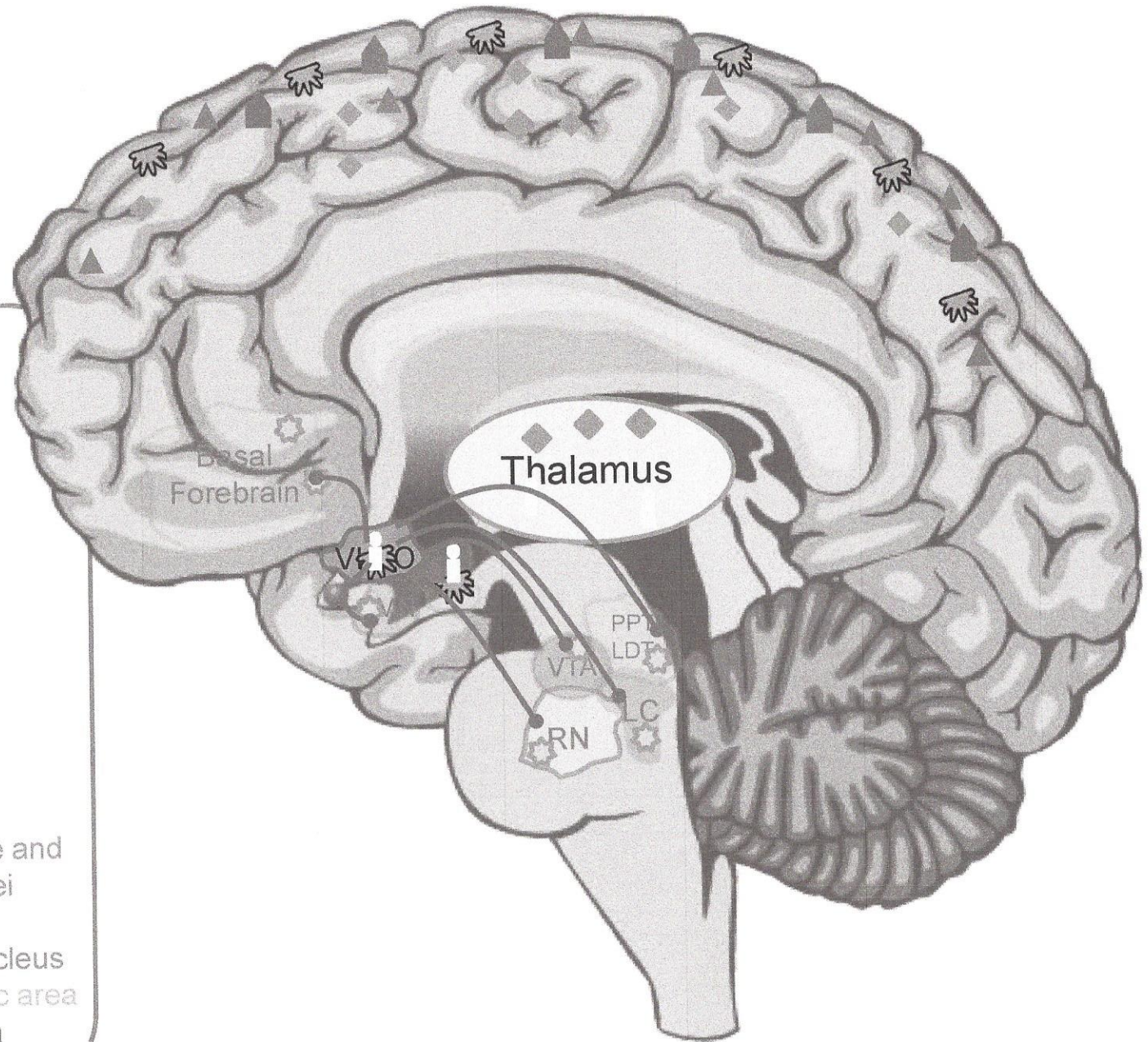
LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculo pontine and laterodorsal tegmental nuclei
RN: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area










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-  Hypocretin
-  Acetylcholine
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-  Norepinephrine
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-  Histamine

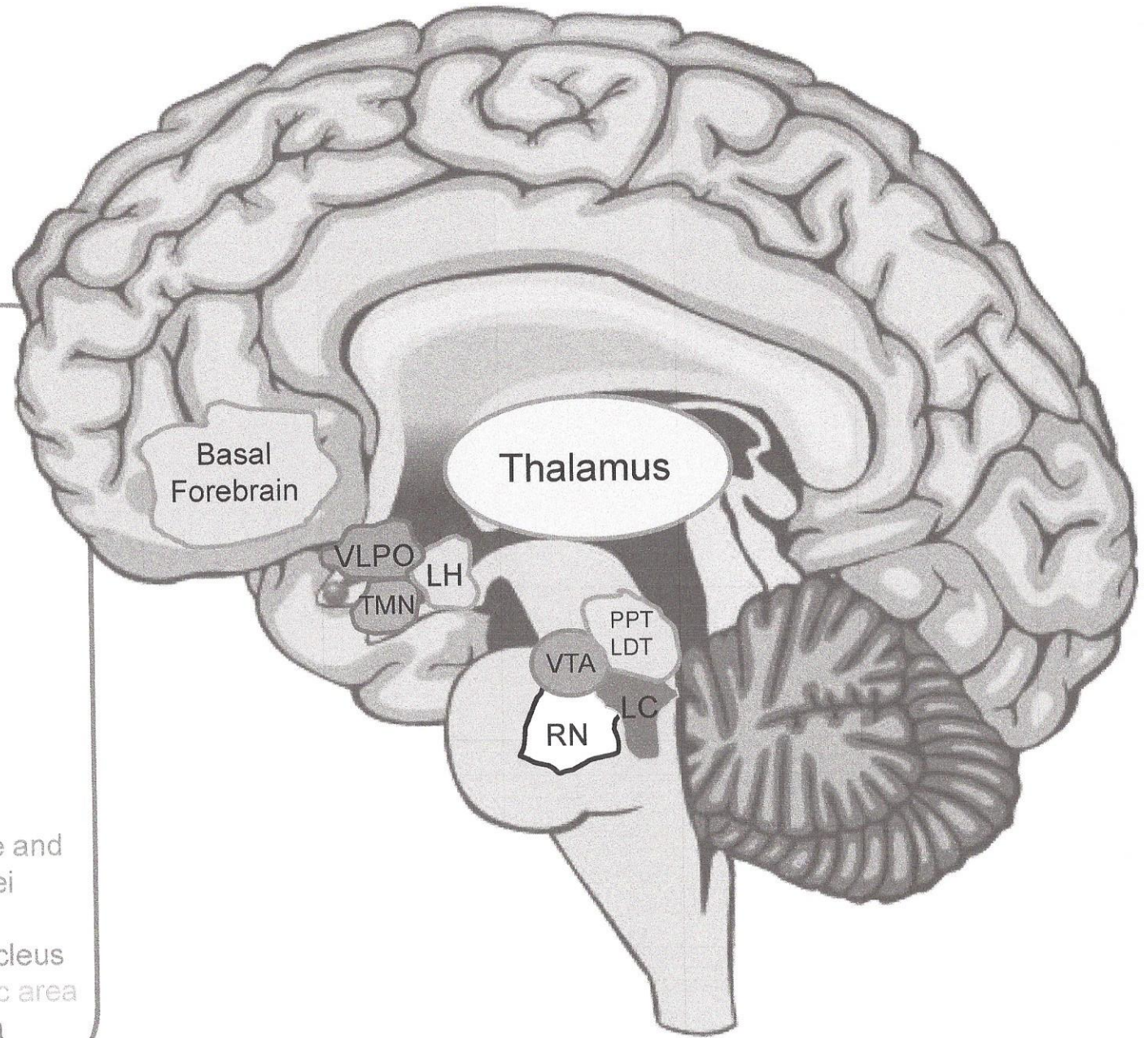
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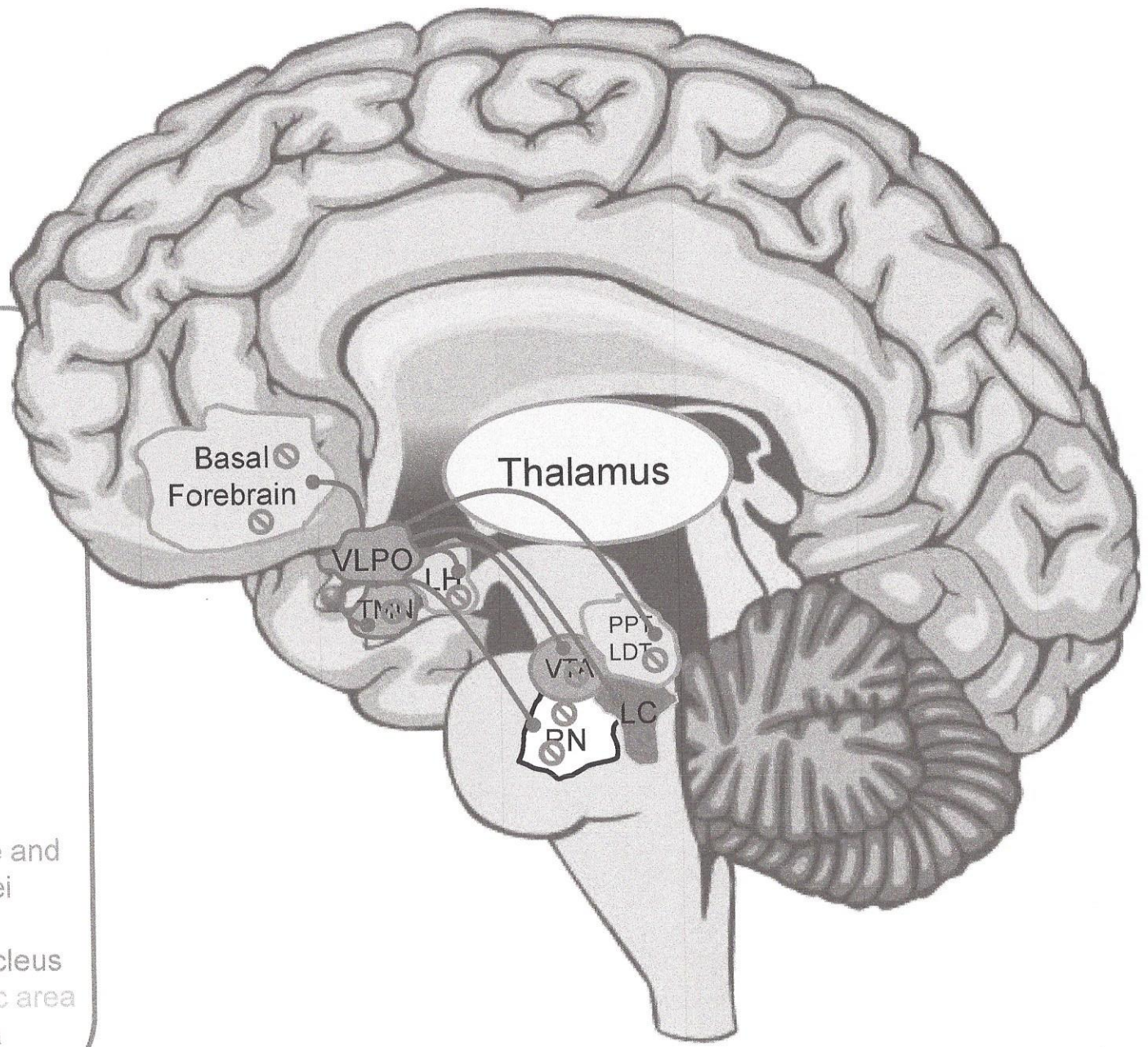
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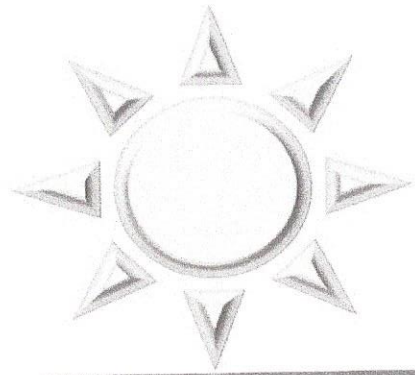




-  GABA/Galanin
-  Hypocretin
-  Acetylcholine
-  Dopamine
-  Norepinephrine
-  Serotonin
-  Histamine

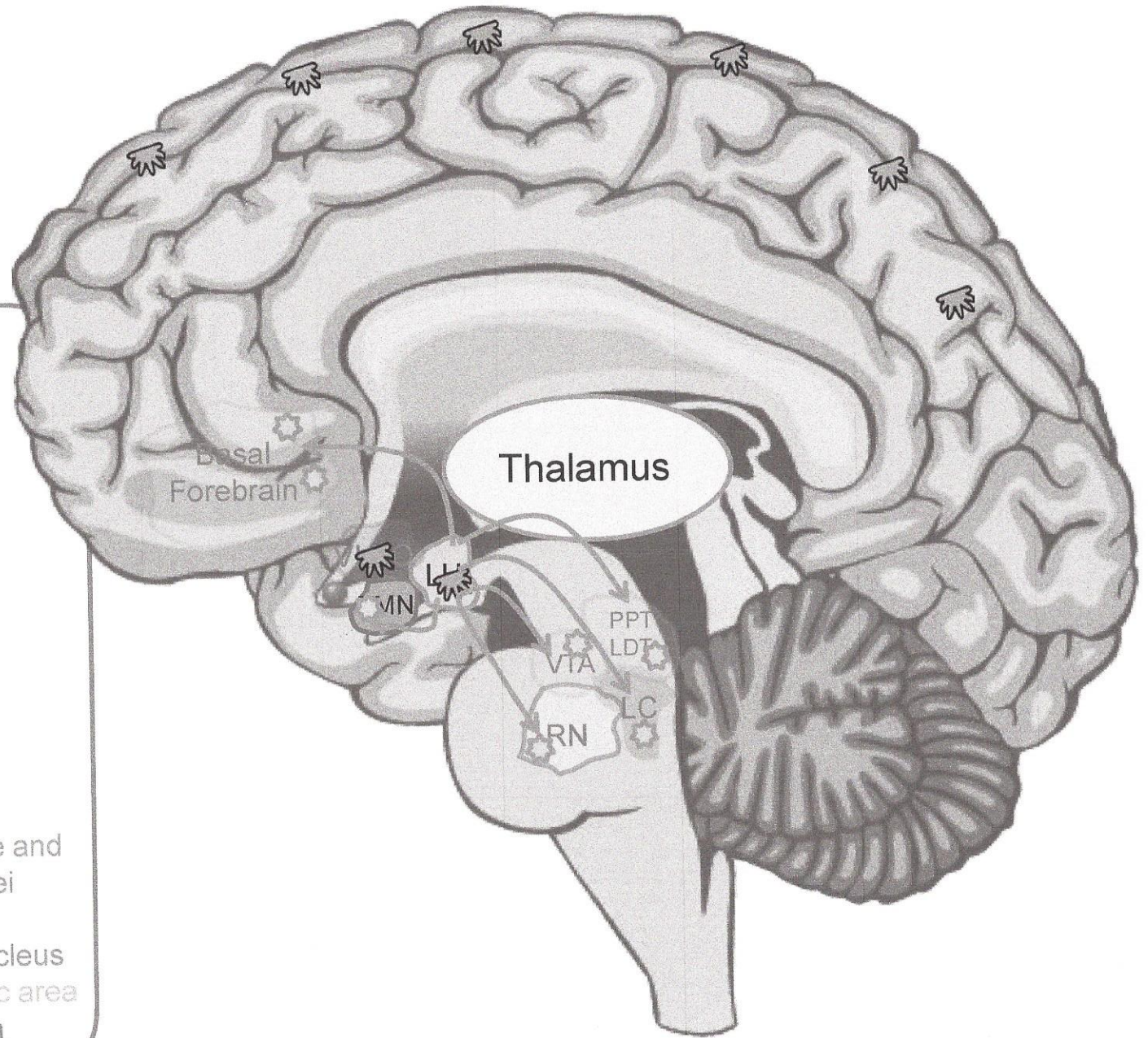
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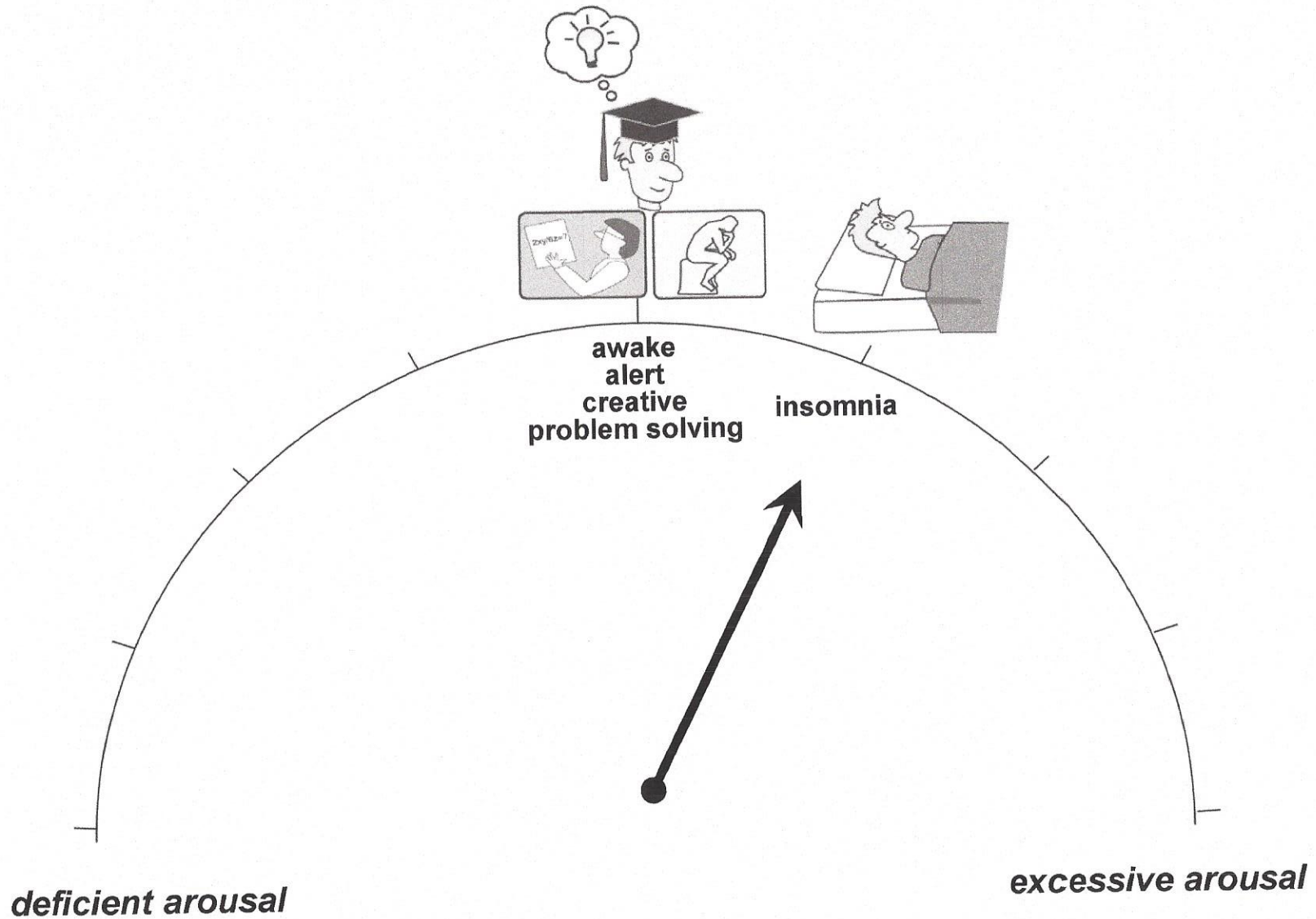


Tools for Assessing Sleep-Wake Disorders

- Polysomnography
 - Electroencephalogram (EEG): brain activity
 - Electrooculogram (EOG): eye movements
 - Electromyogram (EMG): muscle activity
 - Electrocardiogram (ECG): heart rhythm
- Multiple Sleep Latency Test
 - Uses polysomnography to detect the latency to onset of sleep
- Actigraphy
 - Measures gross motor activity to detect rest/activity cycles
- Sleep/Wake Diary
- Epworth Sleepiness Scale
- Pittsburgh Sleep Quality Index
- Morningness-Eveningness Questionnaire

see appendix for additional details

Insomnia: Excessive Nighttime Arousal



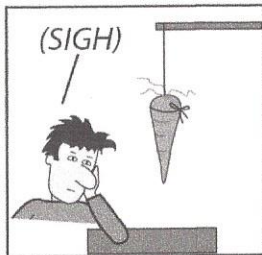
Insomnia: Excessive Nighttime Arousal

- The most common sleep-wake disorder
 - Prevalence: 15% in the adult US population (40 million Americans)
- Affected individuals often complain of poor sleep quality or duration, difficulty falling asleep, nighttime awakenings, or wake times that are earlier than desired
- Importantly, the vast majority of the time, insomnia is comorbid with medical and psychiatric disorders

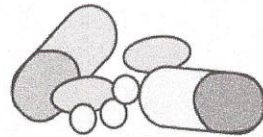
Conditions Associated With Insomnia



Substance Abuse



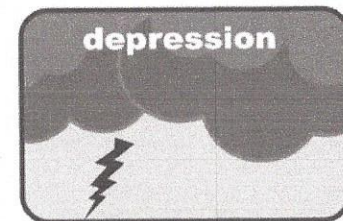
Behavioral/Psychological Causes



Medication Side Effects

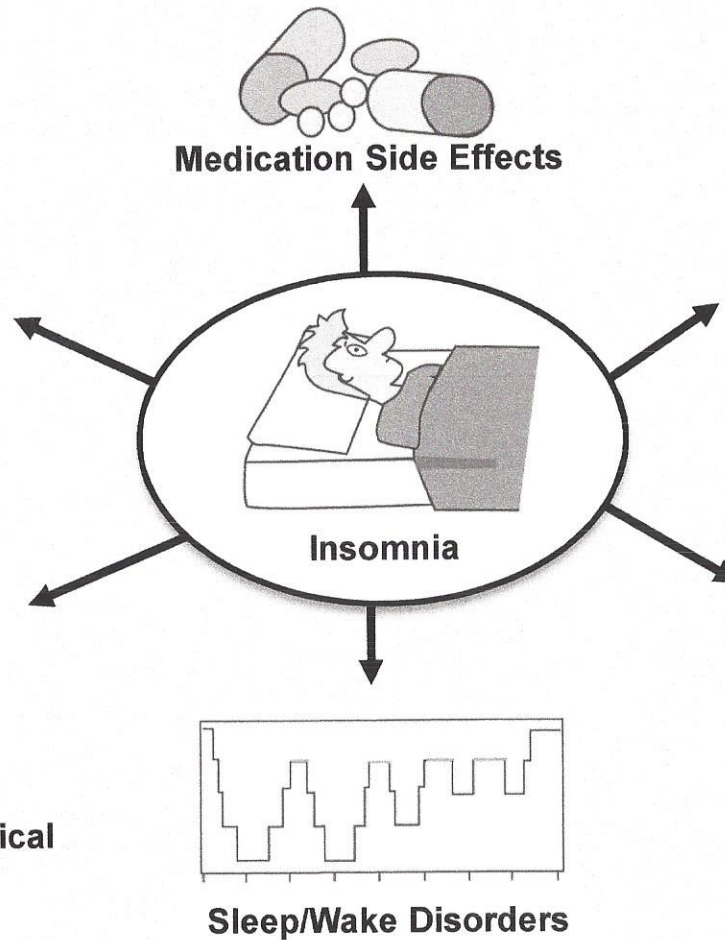


Medical Conditions



Psychiatric Conditions

- 2x more likely to develop **anxiety**
- 4x more likely to develop **depression**
- 7x more likely to develop **SUD**



Dresler M et al., Pharmacol Ther 2014;141:300-34; Espana, Scammell. Sleep 2011;34(7):845-58; Morin CM, Benca R. Chronic insomnia. Lancet 2012;379:1129-41

Insomnia: DSM-5 Diagnostic Criteria

- Complaint of dissatisfaction with sleep quantity or quality, associated with at least one of the following symptoms:
 - Difficulty initiating sleep
 - Difficulty maintaining sleep
 - Early-morning awakening with inability to return to sleep
- Sleep disturbance causes distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
- Disturbance occurs at least 3 nights per week and is present for at least 3 months
- Disturbance is not attributable to the physiologic effects of a substance or a coexisting medical or mental disorder

Insomnia: Differential Diagnosis

- Evaluate sleep quality and sleepiness
 - e.g., Epworth Sleepiness Scale
 - 24-hr sleep-wake diary maintained for 2 wks
- Complete history and both physical and psychiatric exams
 - Evaluate risk factors for sleep apnea (neck circumference, BMI, etc.)
 - Evaluate comorbid medical conditions and medication use
 - Psychiatric evaluation should focus on mood, anxiety, and memory
- Actigraphy is indicated to rule out circadian rhythm disorders
- Polysomnography
 - Not indicated in the routine evaluation of insomnia
 - May be useful for patients with comorbid sleep disorders (e.g., apnea, RLS), when initial diagnosis is uncertain, when treatment fails, or if arousals occur with violent or injurious behavior

Insomnia Severity Index

Please rate the **CURRENT** (*i.e.*, **LAST 2 WEEKS**) **SEVERITY** of your insomnia problem(s).

Insomnia problem	None	Mild	Moderate	Severe	Very severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problem waking up too early	0	1	2	3	4
4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?					
Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied	
0	1	2	3	4	
5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?					
Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable	
0	1	2	3	4	
6. How WORRIED/DISTRESSED are you about your current sleep problem?					
Not at all Worried	A Little	Somewhat	Much	Very Much Worried	
0	1	2	3	4	
7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g., daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood) CURRENTLY?					
Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering	
0	1	2	3	4	

Total score categories:

0–7 = No clinically significant insomnia

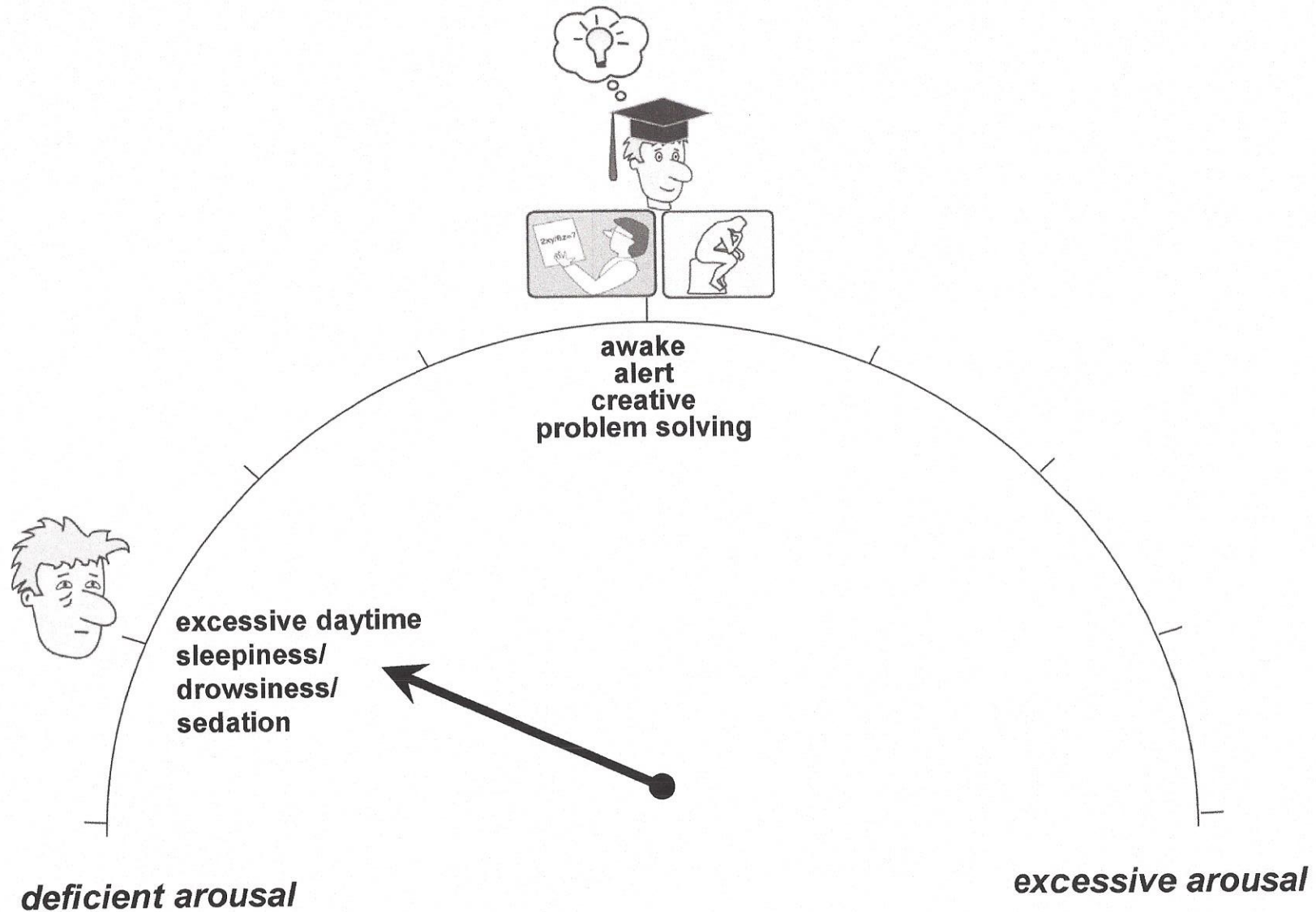
8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Bastien CH et al., Sleep Med 2001;2(4):297-307.

Excessive Daytime Sleepiness: Deficient Daytime Arousal



Clinical Evaluation of Hypersomnia

Clinical evaluation: Evaluate cataplexy, nature and severity of sleepiness (exclude fatigue), sleep paralysis, hypnagogic hallucinations, or automatic behaviors.
Rule out obstructive sleep apnea, insufficient sleep syndrome, or a circadian rhythm disorder.

Definite Cataplexy

Type 1 Narcolepsy/Hypocretin deficiency

PSG/MSLT for objective documentation; may allow for more aggressive treatment later.

If MSLT negative, interpret with clinical context; cataplexy may be sufficient to diagnose narcolepsy. Consider repeat MSLT.

Consider measuring Hypocretin-1 if:

1. Psychotropic medications
2. Associated sleep disorders
3. Confounding neurological or psychiatric disorders
4. Very young child

No Cataplexy or Atypical Cataplexy

Type 2 or Other Hypersomnia

Preceded by PSG to rule out other sleep disorders; document adequate nocturnal sleep. No shift work.

If other sleep disorder (e.g. OSA), then treat before MSLT.

Positive MSLT MSL ≤ 8 minutes and ≥ 2 SOREMPs: narcolepsy without cataplexy

No cataplexy, many SOREMPs: consider CSF hypocretin.

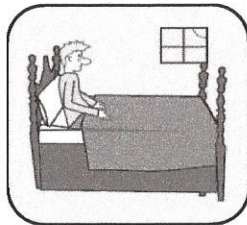
Differential Diagnosis of Hypersomnia

	Subjective Sleepiness	MSLT Sleep Latency	SOREMPs	Hcrt/Ox Levels
Narcolepsy with cataplexy	✓	≤ 8 min	≥ 2	Low ≤ 110 pg/mL
Narcolepsy without cataplexy	✓	≤ 8 min	≥ 2	Normal 200-700 pg/mL
Idiopathic hypersomnia	✓	≤ 8 min	≥ 2	Normal 200-700 pg/mL
Recurrent hypersomnia	✓ Episodic	Normal between episodes	≥ 2	Normal 200-700 pg/mL

Ahmed I et al. Clin Chest Med 2010;31:371-81; Bourgin P et al. Lancet Neurol 2008;7(7):649-62; Dresler M et al. Pharmacol Ther 2014;141:300-34; Mignot EJM. Neurotherapeutics 2012;9:739-52; Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders. 2016

Idiopathic Hypersomnia

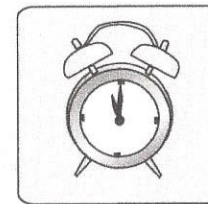
- Sleepiness; no REM abnormalities or SOREMPs; no other likely cause for sleepiness
- Typically increased sleep time (over 10 hours daily); if not, $MSLT\ SL \leq 8\ min$, 0-1 SOREMP
- Prevalence unknown; considered rare in its typical form



Non-refreshing
sleep



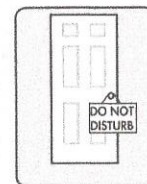
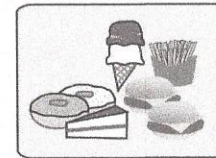
Excessive daytime
sleepiness



Long (>10) or normal
sleep duration

Recurrent Hypersomnia

- Continuing excessive daytime sleepiness
 - May be associated with menstruation in women
- Kleine-Levin syndrome
 - Excessive daytime sleepiness
 - Cognitive and mood disorders
 - Compulsive eating
 - Hypersexuality
 - Disinhibited behavior



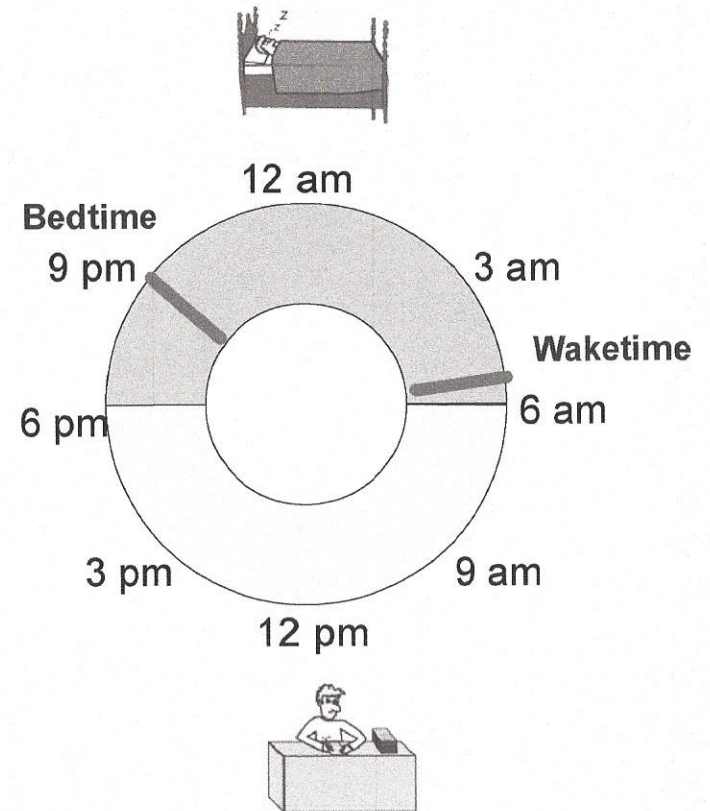
Narcolepsy

- Narcolepsy is characterized by:
 - Excessive daytime sleepiness
 - Intrusion of sleep during periods of wakefulness
 - Abnormal REM sleep, including periods of REM occurring at the onset of sleep (SOREMPs)
- Cataplexy, or loss of muscle tone triggered by emotions, may also be present.
- Hypnagogic hallucinations, which are present upon waking, are also often present

Circadian Rhythm Disorders

- Dyssynchrony between the internal clock and external cues that signal "daytime" and "nighttime."
- Difficulty maintaining a sleep/wake cycle within the typical 24-hour period
- Disorders include:
 - Shift work disorder
 - Advanced sleep phase disorder
 - Delayed sleep phase disorder
 - Non-24-Hour Sleep-Wake disorder

Desired Sleep/Wake Schedule



Shift Work Disorder (SWD)

Insomnia or excessive sleepiness temporarily associated with a recurring work schedule that overlaps with the usual time for sleep

15-25% of the workforce in the US are shift workers including those who work:

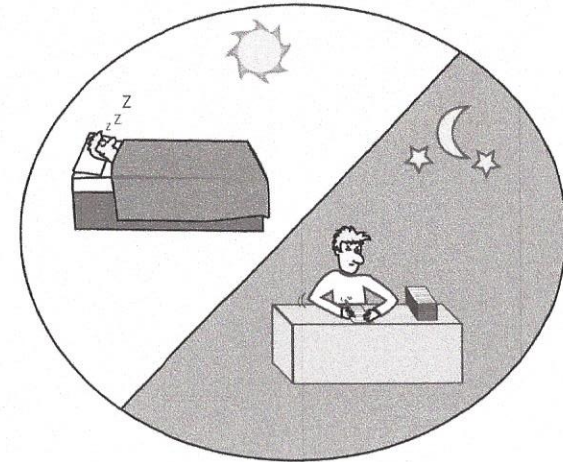
- night shifts
- evening shifts
- rotating shifts

10-32% of shift workers develop SWD

SWD associated with increased risk of cardiometabolic issues, cancer, gastrointestinal diseases, and mood disorders

Shift Work Diagnosis

- Symptoms associated with shift work schedule are present for ≥ 1 month
- Sleep log or actigraphy monitoring (with sleep diary) for at least 7 days demonstrates disturbed sleep (insomnia) as well as circadian and sleep/time misalignment
- Sleep disturbance is not due to another current sleep disorder, medical disorder, mental disorder, substance use disorder, or medication use



Advance/Delayed Sleep Phase Disorders

PATIENT CASE

Diagnosis

- Rule out other sleep/wake disorders, such as insomnia
- Sleep diary and/or actigraphy for at least a week
- Administration of the Morningness-Eveningness Questionnaire (MEQ)

R_x

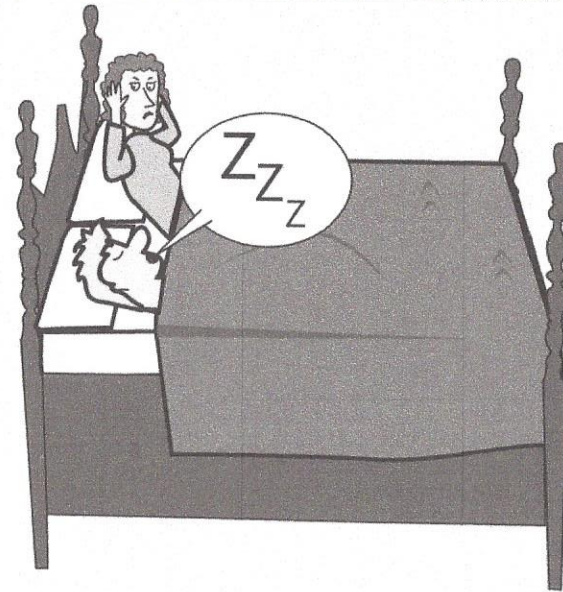
Treatment

- Bright light therapy
- Chronobiotics (including melatonin, ramelteon, or tasimelteon)
- Armodafinil/modafinil
- Structured sleep/wake schedules

Obstructive Sleep Apnea (OSA)

Pathophysiology

- Partial/full collapse of upper airway
- Narrowing may occur at different levels
- Muscle tone, airway reflexes
- Metabolic abnormalities in frontal lobe white matter and hippocampus



Clinical Features

- Loud snoring
- Obesity
- Hypertension
- Neck >17"
- Enlarged tonsils
- Loss of interest
- Excessive daytime sleepiness
- Fatigue
- Depression

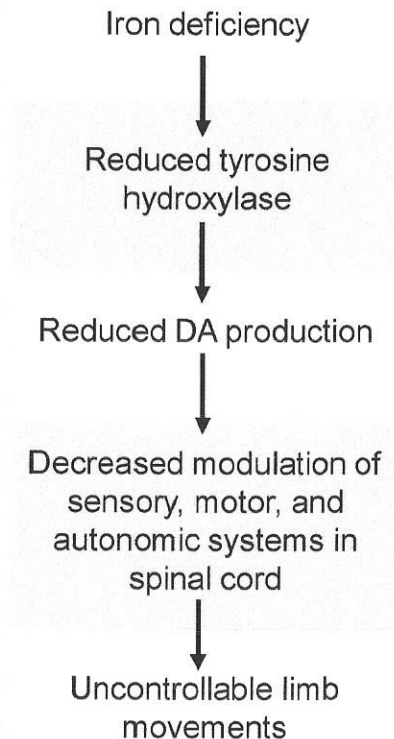
Diagnosis

- Polysomnography (PSG)
 - Frequency of obstructive events measured with:
 - Apnea-Hypopnea Index (AHI)
 - Respiratory Disturbance Index (RDI)
- see appendix*

Restless Legs Syndrome (RLS)

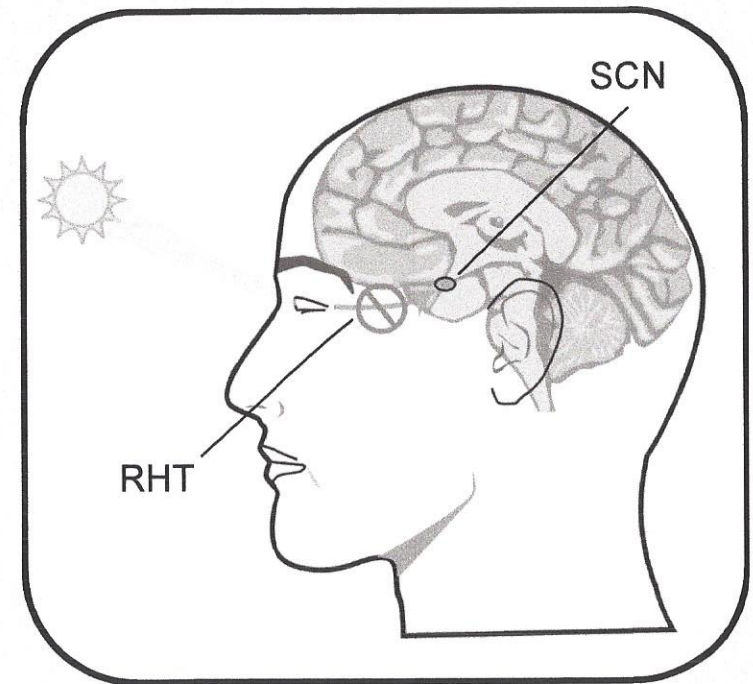
- Urge to move the lower limbs
- Patients often experience both excessive daytime sleepiness and insomnia
- Deficiencies in dopamine and iron
- **Diagnosing:** Cambridge-Hopkins Diagnostic Questionnaire for RLS (CH-RLSq)
- Treatment options target the dopaminergic system
- Iron supplementation may be effective

Neurobiology of RLS



Non-24-Hour Sleep-Wake Disorder

- Free-running internal clock
- Leads to irregular sleep/wake patterns that may cause both insomnia and excessive daytime sleepiness
- Primarily affects individuals who are visually impaired
- Melatonin MT1 and MT2 receptor agonist



SCN: suprachiasmatic nucleus
RHT: retinohypothalamic tract

Bonacci JM et al. J Pharm Pract 2015;28(5):473-8;
Carocci A et al. Pharmacol Adv Applications 2014;6:127-37;
Laudon M, Frydman-Marom A. Int J Mol Sci 2014;15:15924-50;
Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders. 2016

TREATMENT OF SLEEP/WAKE DISORDERS

Commonly Used Psychotropics That May Affect Sleep and Waking

Drug Type	Pharmacological Effect	Neurobiological Mechanism	Clinical Effects
SSRIs	Increase 5HT	5HT inhibits REM sleep	Decreased REM sleep
TCAs	Increase 5HT and NE	5HT and NE inhibit REM	Decreased REM sleep
Traditional amphetamine-like stimulants	Increase DA and NE	Increased DA and NE signaling	Increased wakefulness
Wake-promoting, nontraditional stimulants	Increase DA	Increased DA signaling	Increased wakefulness
Benzodiazepines	Enhance GABA signaling GABA-A receptors	GABA inhibits the arousal systems	Increased sleep
Nonbenzodiazepine sedatives	Enhance GABA signaling GABA-A receptors	GABA inhibits the arousal systems	Increased sleep
Antihistamines	Block HA H1 receptors	Reduced HA signaling	Increased sleep
Typical antipsychotics	Block DA receptors	Reduced DA signaling	Increased sleep

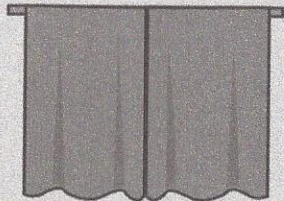
Espana, Scammell. Sleep 2011;34(7):845-58.

Sleep-Wake Hygiene

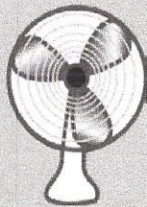
Sleep Time



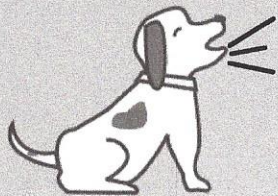
No stimulants before bed



Dark room

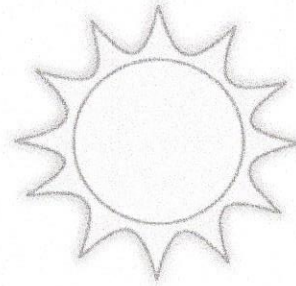


Cool environment

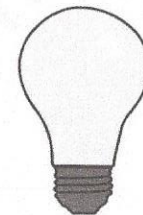


No disturbances

Wake Time



Activity

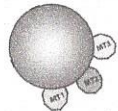


Bright Light

Resetting Circadian Rhythms

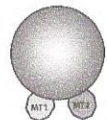
Melatonergic Agents

Promote sleep by resetting the sleep/wake cycle



Melatonin

- Acts at MT1 and MT2 receptors as well as at the MT3 site
- Available over the counter

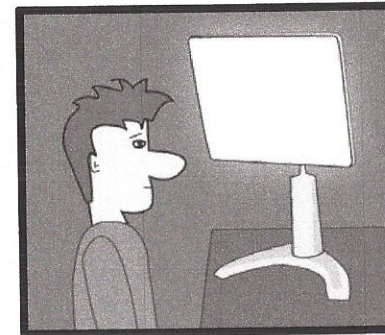


MT1 and MT2 Receptor Agonists

- Improve sleep onset
 - **ramelteon**: FDA approved for the treatment of insomnia
 - **tasimelteon**: FDA approved Non-24-Hour Sleep-Wake disorder

Bright Light Therapy

Suppresses melatonin release



- Treatment with 10,000 lux, bright, blue light for 30 minutes a day may be used to reset circadian rhythms
- Shown to improve performance, alertness, and mood during the night shift can be improved in shift workers

Bonacci JM et al. J Pharm Pract 2015;28(5):473-8; Crowley SJ et al. Sleep 2004;27(6):1077-87; Stahl's Essential Psychopharmacology. 4th ed. 2013

Promoting Sleep

Enhance

⊘ GABA/galanin

Inhibit

○ hypocretin/orexin

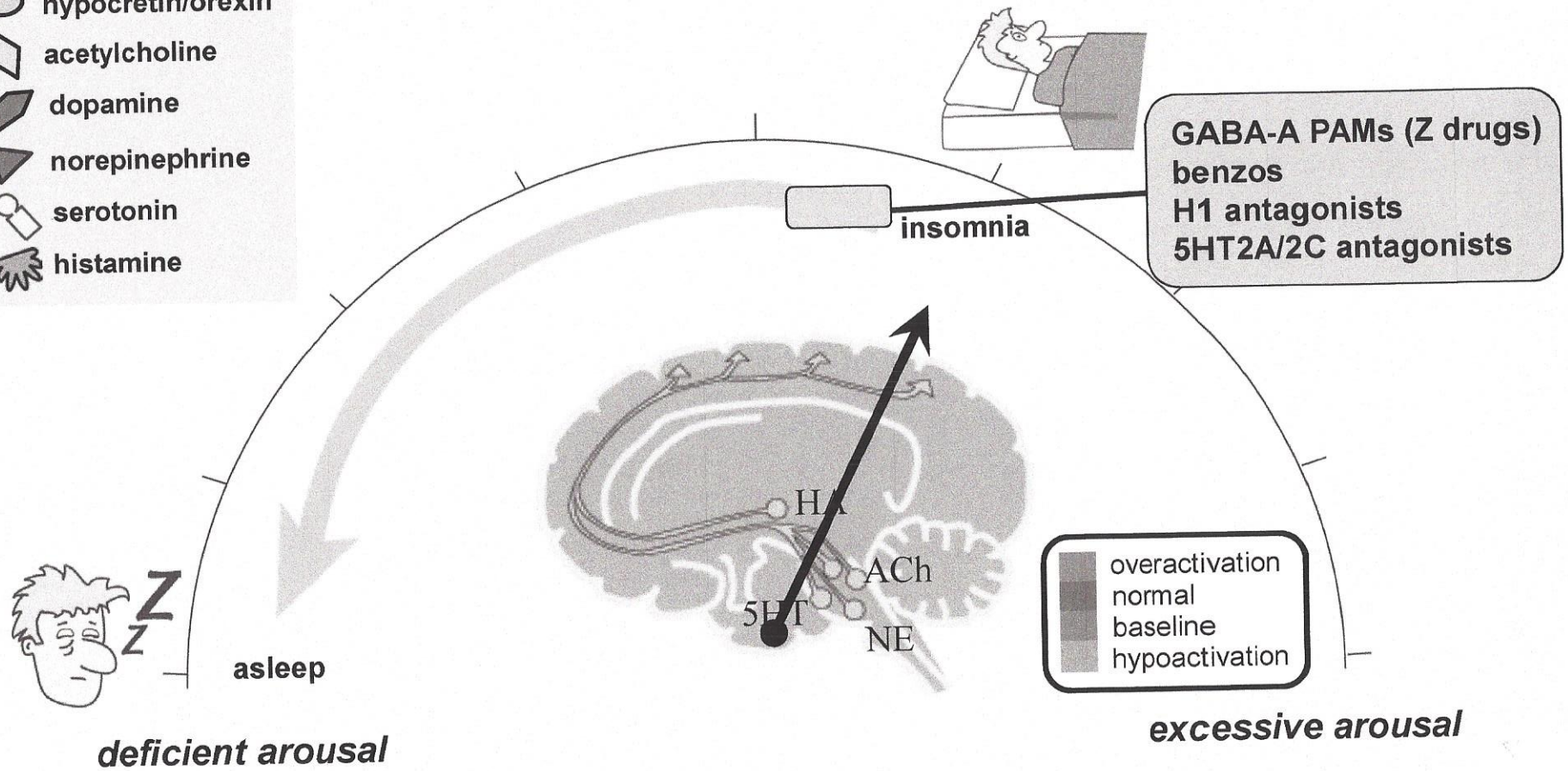
◇ acetylcholine

◀ dopamine

▲ norepinephrine

⊘ serotonin

✎ histamine



Pharmacological Treatments for Insomnia

Pharmacological Agent	FDA-Approved for Insomnia
Benzodiazepine Hypnotics	
Estazolam	✓
Flurazepam	✓
Quazepam	✓
Temazepam	✓
Triazolam	✓
Nonbenzodiazepine Hypnotics	
Eszopiclone	✓
Zaleplon	✓
Zolpidem	✓
Antidepressants	
Doxepin	✓
Trazodone	

Pharmacological Agent	FDA-Approved for Insomnia
Hypocretin/Orexin Antagonist	
Suvorexant	✓
Melatonin Receptor Agonists	
Melatonin	
Ramelteon	✓
Tasimelteon	
Antipsychotics	
Quetiapine	
Olanzapine	
Anticonvulsants	
Clonazepam	
Gabapentin	
Tiagabine	

Nonpharmacological Treatments for Insomnia

- Relaxation training
 - Aimed to reduce somatic tension and intrusive thoughts that interfere with sleep
- Stimulus control therapy
 - Get out of bed if not sleepy; use bed only for sleeping; no napping
- Sleep restriction therapy
 - Limit time spent in bed to produce mild sleep deprivation; results in more consolidated sleep
- Intensive sleep retraining
 - 25-hour sleep deprivation period in which the patient is given 50 sleep onset trials but awoken following 3 minutes of sleep
- Cognitive behavioral therapy
 - Reduce negative attitudes and misconceptions about sleep

Harris J et al. Sleep 2012;35(1):49-60;
Morin CM, Benca R. Chronic insomnia. Lancet 2012;379:1129-41

Promote Wakefulness

Inhibit

⊖ GABA/galanin

Enhance

○ hypocretin/orexin

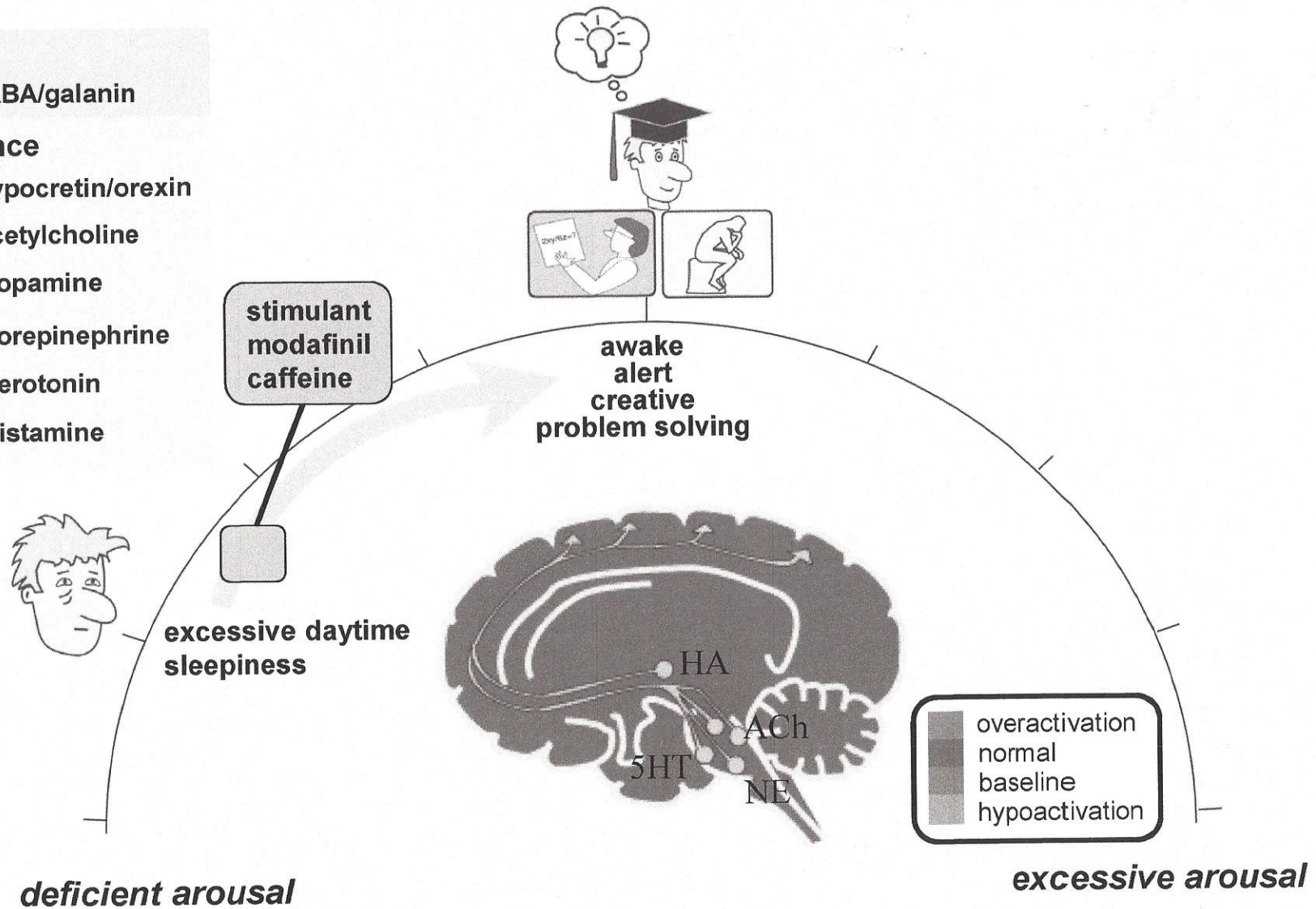
◇ acetylcholine

▴ dopamine

▾ norepinephrine

⊖ serotonin

✎ histamine



Pharmacological Treatments for Hypersomnia

	Modafinil	Armodafinil	Stimulants	Caffeine	Melatonin	Sleep aids	Antidepressants
Narcolepsy	X	X	X	X			X
Idiopathic hypersomnia	X	X	X	X			X
OSA	X	X	X	X			X
RLS	X	X	X	X		X	X
Circadian rhythm disorders	X	X	X	X	X	X	

FDA-approved for this indication

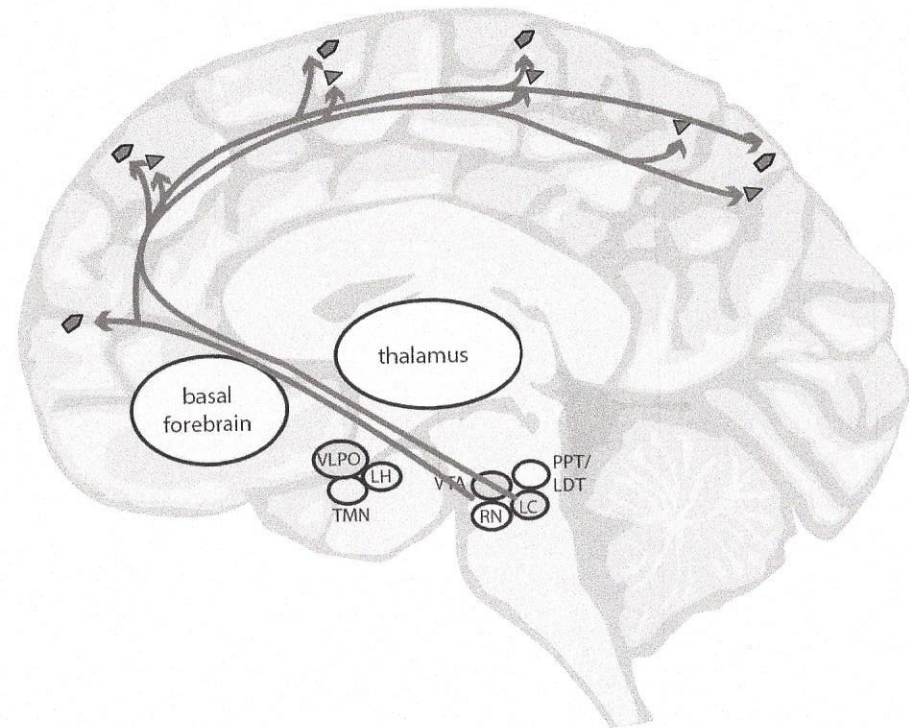
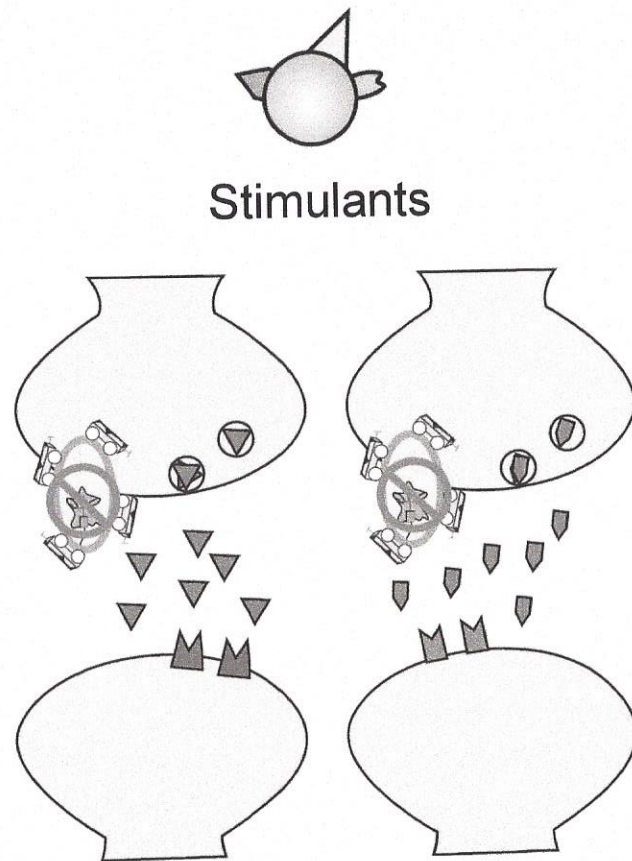
Pharmacological Treatments for Hypersomnia

	Excessive Daytime Sleepiness	Cataplexy
Stimulants		
Amphetamine	*√	
Methylphenidate	*√	
Lisdexamfetamine	√	
Atomoxetine	√	√
Antidepressants		
TCA - Protriptyline		√
TCA - Imipramine		√
TCA - Clomipramine		√
TCA - Desipramine		√
SNRI - Venlafaxine		√
SNRI - Duloxetine		√
SSRI - Fluoxetine		√
MAOI - Selegiline	√	√
Other Agents		
Modafinil/Armodafinil	*√	
Sodium Oxybate	*√	*√
Caffeine	√	

* Indicates FDA approval for this indication

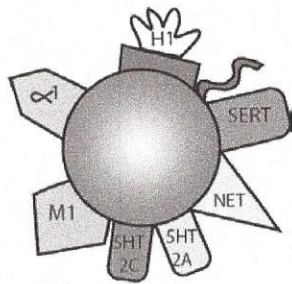
Stahl's Illustrated Sleep and Wake Disorders. 2016

Promoting Wakefulness: Stimulants



Hirai N, Nishino S. *Curr Treatment Options Neurol* 2011;13:437-57;
Mignot EJM. *Neurotherapeutics* 2012;9:739-52;
Stahl SM, Morrissette DA. *Stahl's Illustrated Sleep and Wake Disorders*. 2016

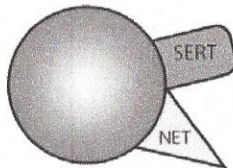
Promoting Wakefulness: Antidepressants



TCA



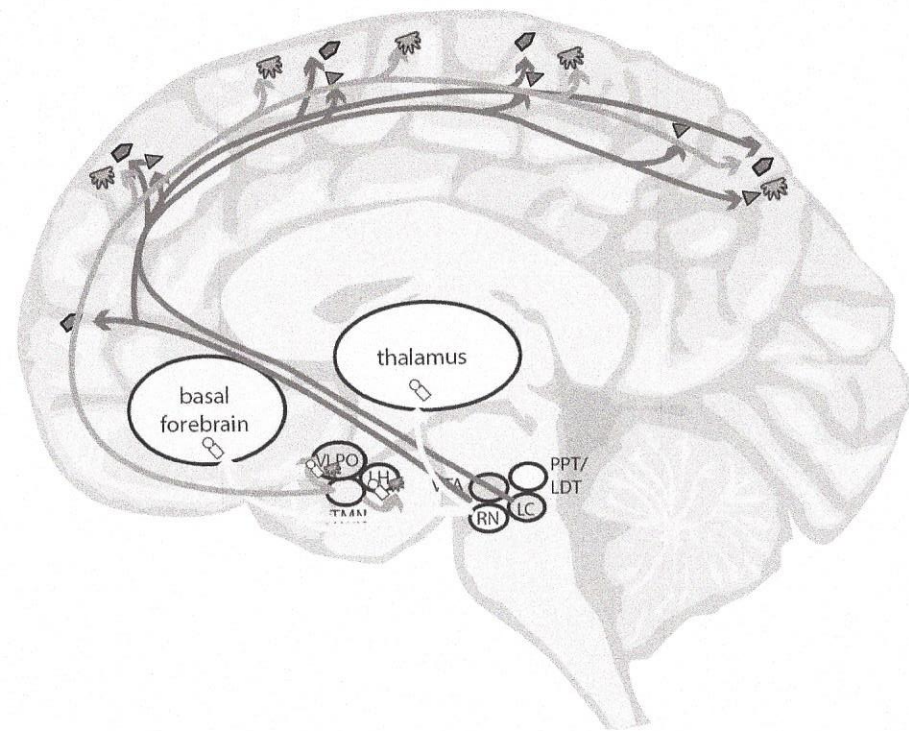
SSRI



SNRI



MAOI

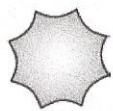


Ahmed I, Thorpy M. Clin Chest Med 2010;31:371-81;

Mignot EJM. Neurotherapeutics 2012;9:739-52;

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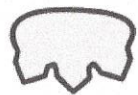
Promoting Wakefulness: Other Agents



Modafinil/ Armodafinil

- Reducing excessive sleepiness in patients with narcolepsy and shift work sleep disorder
- Reducing excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome

Dosage:
150–250 mg/day



Sodium Oxybate

- Reducing excessive sleepiness in patients with narcolepsy
- Cataplexy in patients with narcolepsy

Dosage:
6 - 9 g/night in 2
doses 2.5 - 4
hours apart



Caffeine

- By blocking adenosine from binding to adenosine 2A receptors, caffeine prevents the lowered affinity of D2 receptors for dopamine.
- The increased GABAergic neurotransmission disinhibits downstream excitatory glutamatergic neurotransmission

Darwish M et al. Clin Ther 2010;32(12):2074-87; Morrissette DA. CNS Spectrums 2013;18(suppl 1):45-53;
Adenuga O, et al. Curr Treatment Options Neurol 2014;16:302; Stahl SM, Morrissette DA. Stahl's
Illustrated Sleep and Wake Disorders. 2016

Treating Obstructive Sleep Apnea (OSA)

First-line treatment option: Continuous Positive Airway Pressure

- Adherence rates are poor (54%)
- Other Treatment Options:
 - Bilevel positive airway pressure (BPAP)
 - Auto-titrating positive airway pressure (APAP)
 - Oral appliances designed to stabilize the jaw and/or tongue during sleep
 - Various surgeries aimed at correcting physical attributes that may contribute to OSA
- Behavioral Interventions
 - Weight loss (BMI <25)
 - Exercise
 - Avoidance of alcohol and sedatives at bedtime
 - Positional therapy

Aurora RN et al. Sleep 2012;35(1):17-40; Epstein LJ et al. J Clin Sleep Med 2009;5(3):263-76; Norman D et al. J CA Dent Assoc 2012;40(2):141-9; Rogers RR. J CA Dent Assoc 2012;40(2):151-7; Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders. 2016

Treating Restless Legs Syndrome (RLS)

RLS Treatment	FDA-Approved
Dopamine Agonists	
Ropinirole	√
Pramipexole	√
Carbidopa-levodopa	
Iron supplementation	
GABAergic Agents	
Gabapentin enacarbil	√
Pregabalin	
Opiates	
Benzodiazepines	

Ahmed, Guilleminault. *Curr Pharm Des* 2011;17:1418-25; Freedom. *Dis Month* 2011;57:438-47; Miletic, Relja. *Collegium Antropologicum* 2011;35(4):1339-47; Stahl SM, Morrissette DA. *Stahl's Illustrated Sleep and Wake Disorders*. 2016